



# Management of Functional Constipation in Children: Therapy in Practice

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Published online: 11 August 2015

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**Abstract** Functional constipation is a common healthcare problem among children worldwide and accounts for high healthcare usage and costs. Functional constipation is a clinical diagnosis; the evaluation primarily consists of a thorough medical history and a complete physical examination. Additional investigations are not necessary in most cases. Treatment consists of non-pharmacological and pharmacological interventions. Non-pharmacological interventions involve education and demystification, toilet training (with a reward system), and a defecation diary. Pharmacological treatment comprises three steps: disimpaction, maintenance treatment, and weaning. The treatment of first choice is oral laxatives, preferably polyethylene glycol. When this is insufficient, other therapeutic agents are available. This review discusses the evaluation and management of functional constipation in the pediatric population and provides a summary of drug treatment options.

## Key Points

Functional constipation in children is a commonly occurring disorder. It is a clinical diagnosis based on medical history and physical examination.

In the treatment of functional constipation, the medication of first choice for both disimpaction and maintenance treatment is polyethylene glycol.

Other therapeutic agents (e.g., stimulant laxatives or lubricants) may be useful as additional or second-line therapy if adequate treatment with oral laxatives is insufficient.

## 1 Introduction

Functional constipation (FC) is a common pediatric healthcare problem worldwide, with reported prevalences ranging between 0.7 and 29.6 % and a mean female-to-male ratio of 2.1:1 [1]. FC is characterized by infrequent bowel movements, hard and/or large stools, painful defecation, and fecal incontinence, and is often accompanied by abdominal pain [2]. These symptoms can have a significant impact on a child's well-being and health-related quality of life [3–9]. It is estimated that constipation in children accounts for 3 % of visits to a general pediatrician and up to 25 % of visits to a pediatric gastroenterologist in the USA [10]. Furthermore, healthcare costs for children with constipation are higher than those for control subjects, mostly because of ambulatory care costs and, to a lesser degree, costs related to hospitalizations and emergency room visits [11]. Estimations of the economic burden

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caused by childhood FC vary between studies [12, 13]. In the USA, the total additional costs for childhood constipation have been estimated to be US\$3.9 billion per year [13]. Furthermore, the same study revealed that the mean total unadjusted annual expenditure for children with constipation was three times higher than that for children without constipation (US\$3430/year versus US\$1099/year) [13].

This review focuses on the current approach to management of FC in the pediatric population and provides practical guidance, including a summary of drug treatment options.

## 1.1 Definition

To define FC and other functional defecation disorders in children, the Rome III criteria were defined by a group of pediatric gastroenterology experts in 2006 [14]. The Rome III criteria for FC in children differentiate between children up to 4 years of age and children aged  $\geq 4$  years. These criteria are listed in Table 1. In the spring of 2016, the newly revised Rome IV criteria are expected to be published.

FC not responding to optimal conventional treatment for at least 3 months is defined as intractable constipation [15].

## 1.2 Pathophysiology

In approximately 95 % of children with constipation, no organic cause can be identified [15]. These children suffer from FC. In the remainder of cases, constipation has an organic cause, such as a metabolic or endocrine disorder, anorectal anomalies, neuromuscular diseases, or Hirschsprung's disease [16].

The pathophysiology of FC is still incompletely understood but is likely to be multifactorial. One important etiological factor, especially in young children, is withholding behavior, frequently occurring after a negative experience—e.g., a hard, painful, and/or frightening bowel

movement [17]. Stool-withholding behavior can lead to fecal impaction—the presence of a large fecal mass in either the rectum or the abdomen. Moreover, fecal impaction often causes overflow fecal incontinence, which is involuntary loss of soft stools that pass an obstructing fecal mass.

Psychosocial factors, such as major life events, may play an important role in the pathophysiology of FC. Furthermore, behavioral disorders, such as autism spectrum disorders and attention deficit/hyperactivity disorder, are associated with a higher risk of childhood constipation [18, 19]. Lastly, factors such as socioeconomic status, educational level, and parental child-rearing attitudes have been designated as influencing factors in the pathophysiology of FC in children [1, 20].

## 2 Evaluation

Evaluation of childhood constipation primarily consists of a thorough medical history and a complete physical examination [15]. In most cases, additional investigations are not necessary.

### 2.1 Medical History

The medical history should focus on the child's bowel habits. Questions should address the defecation frequency, number of episodes and timing of fecal incontinence, stool consistency, withholding behavior, and painful and/or hard bowel movements (see Table 1). The Modified Bristol Stool Form Scale for Children can be used to define stool consistency [21]. A daily bowel diary can be useful to gather more reliable information about a child's bowel habits, since recall of bowel habits has proven to be inaccurate [22]. Furthermore, information has to be sought on coexistence of abdominal pain, dietary history, changes in appetite, the presence of nausea and/or vomiting, and other accompanying symptoms. Alarm symptoms suggestive of

**Table 1** Rome III criteria for functional constipation [14]

Age <4 years <sup>a</sup>	Developmental age of $\geq 4$ years <sup>b</sup>
1. <3 defecations per week	1. <3 defecations in the toilet per week
2. $\geq 1$ episode of fecal incontinence per week after acquisition of toileting skills	2. $\geq 1$ episode of fecal incontinence per week
3. History of excessive stool retention	3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements	4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum	5. Presence of a large fecal mass in the rectum
6. History of large diameter stools, which may obstruct the toilet	6. History of large diameter stools, which may obstruct the toilet

<sup>a</sup> Must fulfill  $\geq 2$  criteria for  $\geq 1$  month prior to diagnosis

<sup>b</sup> Must fulfill  $\geq 2$  criteria at least once per week for  $\geq 2$  months prior to diagnosis, with insufficient criteria for diagnosis of irritable bowel syndrome

an organic cause include—but are not limited to—delayed passage of meconium, a history of blood in the stools without the presence of fissures, failure to thrive, and severe abdominal distension [15].

Details about the onset of symptoms, duration of symptoms, and precipitating factors can provide more insight into the pathophysiology. The duration until passage of the first meconium, the presence of fissures during infancy, and feeding-type-change-related defecation alterations in the past may provide valuable insights. It is also important to obtain information about the child's age at successful toilet training. Special attention to psychosocial problems and life events is warranted. Often, the start of symptoms coincides with life events such as the divorce of parents or the birth of a younger sibling.

A detailed medication history should include the use and efficacy of oral laxatives, enemas, and behavioral treatment, and the use of other medication that may influence bowel movements.

For an elaborate disquisition on possible underlying organic causes and alarm symptoms, readers are referred to the evidence-based recommendations published by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) [15].

## 2.2 Physical Examination

Besides assessing weight and height, the physical examination primarily consists of abdominal examination, inspection of the perianal region, examination of the lumbosacral region, and neurological examination.

Abdominal examination mainly focuses on detection of a palpable fecal mass. During perianal inspection, the physician checks for anatomic abnormalities, perianal feces, fissures, scars, and erythema. Fissures may indicate hard and/or large diameter stools. Digital rectal examination provides valuable information on the presence of a rectal fecal mass, anorectal sensation, and sphincter tone [15]. During examination of the lumbosacral region, inspection should focus on the presence of a dimple, a tuft of hair, or a gluteal cleft deviation. A lower limb neuromuscular examination provides information on the neurological integrity of the lumbosacral region.

A history of smearing feces or detection of fissures and hematomas during physical examination should always raise suspicion of sexual abuse. Since the physical examination findings of most pediatric sexual abuse victims are within normal limits, special attention should be paid to abnormal behavior during physical examination (e.g., sexual acting out, extreme fear) [23].

## 2.3 Laboratory Testing

Standard laboratory testing is not necessary in the workup for FC [15].

## 2.4 Radiology

Radiological testing is not required to diagnose childhood constipation [15].

### 2.4.1 Abdominal Radiography

Although it is still frequently used by many physicians, a “plain” abdominal X-ray is not the appropriate tool to demonstrate constipation. Unsatisfactory sensitivity and specificity rates, as well as low inter- and intra-observer reliability, have been reported for the different scoring systems (Barr, Leech, Blethyn) that are used to evaluate these abdominal X-rays [15, 24].

### 2.4.2 Colonic Transit Time

The colonic transit time (CTT) can be determined to evaluate colonic motility. The most widely used method is the marker test; this uses radiopaque markers, which are ingested orally and visualized with an abdominal X-ray [24–26]. Two other, less frequently used, methods to determine the CTT are radionuclide scintigraphy and wireless motility capsules [27]. There is no evidence for routine use of the CTT in the diagnostic workup of FC [15]. An extremely prolonged CTT (>100 h), does however, indicate a severe form of constipation [26]. In situations in which the diagnosis is not clear, a colonic transit study may be useful to discriminate between functional constipation and functional nonretentive fecal incontinence, a disorder characterized by fecal incontinence without signs of constipation [15, 25, 28].

## 2.5 Other Investigations

Other investigations, such as rectal ultrasonography, magnetic resonance imaging (MRI), rectal barostat, barium enemas, anorectal manometry, colonic manometry, colonic scintigraphy, and rectal/colonic biopsies, are sometimes indicated but do not belong in the routine workup of constipation and therefore go beyond the scope of this review.

## 3 Non-Pharmacological Treatment

### 3.1 Education

Education and demystification are the first steps in the non-pharmacological treatment of FC [29]. Information on the

prevalence, symptoms, initiating and perpetuating (risk) factors, treatment options, and prognosis should be provided. Children should be actively involved in this conversation if allowed by their developmental age. A non-accusatory approach of both physicians and parents is of key importance [29]. Children may feel guilty or embarrassed, especially about fecal incontinence episodes; it is therefore important to explain the pathophysiology of overflow incontinence. Childhood constipation is often a long-lasting problem, which should be explained to both parents and patients.

### 3.2 Toilet Training, Reward System, and Defecation Diary

Since the stasis of feces in the rectum can maintain constipation, it is important to evacuate the rectum frequently. In children with a developmental age of  $\geq 4$  years, this can be established by introducing a toilet-training program. Toilet training involves sitting on the toilet for 5 min after each meal to actively try to defecate. By going to the toilet after a meal, the patient takes advantage of the gastrocolic reflex that increases colonic peristalsis upon distension of the stomach, facilitating defecation.

The importance of a relaxed posture during defecation should be explained. To ensure a relaxed posture, foot support (by means of a footstool) is needed for children whose feet do not touch the floor when they are sitting on the toilet. To motivate a child for toilet training, a reward system can be introduced, where small gifts (e.g., stickers) are earned for completing toilet trainings. A daily stool diary can help to objectify the bowel pattern of children with FC. This diary also has a motivating purpose and is a helpful tool to evaluate treatment.

### 3.3 Dietary Fiber, Fluid, and Physical Activity

It has been suggested that children with FC might benefit from additional dietary fiber, extra fluid intake, and/or increased physical activity. These three interventions are discussed below.

#### 3.3.1 Fiber

The normal dietary fiber requirements of children vary from child to child and are age dependent; in children older than 2 years of age, a minimal dietary fiber intake of “age plus 5 g” is usually recommended [30, 31]. A fiber intake below normal limits is associated with FC [32]. Several randomized controlled trials (RCTs) on the effect of dietary fiber in children have been performed [33–37]. However, these studies have used different definitions and outcome measures, and a recent systematic review applying Grading of Recommendations Assessment, Development and Evaluation (GRADE) has shown the overall quality of the evidence to be low [38].

Therefore, normal fiber intake is recommended, but current evidence does not support the use of extra fiber supplements in children with FC with a sufficient dietary fiber intake [15, 38].

#### 3.3.2 Fluid

As with fiber, normal fluid requirements vary from child to child [39]. One study regarding extra fluid intake in children with FC showed insufficient evidence of an advantageous effect on FC symptoms [15, 40]. Therefore, extra fluid intake in children with FC who already have a normal fluid intake is not recommended [15].

#### 3.3.3 Physical Activity

A large prospective birth-cohort study demonstrated that physical activity is associated with a decreased risk of having FC at the preschool stage [41]. However, no RCTs on the effect of increased physical activity on FC in children have been performed [15].

### 3.4 Behavioral Therapy

Behavioral problems occur in approximately one third of patients with FC [42, 43]. This has led to the idea that behavioral therapy might be a therapeutic option in these children. However, in an RCT, behavioral therapy had no advantage over conventional treatment with laxatives in treating childhood constipation [15, 44]. Nevertheless, when behavioral problems are present, behavioral therapy or referral to mental health services, in addition to laxative treatment, should be considered [44].

### 3.5 Biofeedback Training

Approximately 50 % of children with FC have abnormal defecation dynamics [25]. Biofeedback training employs reinforcing stimuli and thereby aims to achieve a recognizable sensation with an appropriate response in children with FC. The long-term goal is to teach children to recognize the sensation by themselves. Several RCTs have assessed the effect of biofeedback training on FC in children. However, there were significant methodological differences between these studies, which makes it difficult to compare them, and the current evidence does not support the use of biofeedback training for the treatment of childhood constipation [15, 45].

## 4 Pharmacological Treatment

Pharmacological treatment for FC consists of treatment with laxatives and involves three steps: disimpaction, maintenance treatment, and, eventually, weaning. The

**Table 2** Pharmacological management of functional constipation in children [15]

Laxative types	Dosage
<b>Oral laxatives</b>	
PEG 3350/4000	Maintenance: 0.2–0.8 g/kg/day in 1–2 doses Fecal disimpaction: 1–1.5 g/kg/day (maximum 6 days)
Lactulose	7 months–18 years: 1–2 g/kg/day in 1–2 doses
Lactitol	1–6 years: 0.5–1 g/kg/day in 2–3 doses 6–12 years: 10–30 g/day in 2–3 doses 12–18 years: 20–60 g/day in 2–3 doses
Bisacodyl	3–10 years: 5 mg/day in 1 dose (at night) >10 years: 5–10 mg/day in 1 dose (at night)
Senna	2–6 years: 2.5–5 mg/day in 1–2 doses 6–12 years: 7.5–10 mg/day in 1–2 doses >12 years: 15–20 mg/day in 1–2 doses
Sodium picosulfate	1 month–4 years: 2.5–10 mg/day in 1 dose 4 to 18 years: 2.5–20 mg/day in 1 dose
Magnesium hydroxide	2–5 years: 0.4–1.2 g/day in 1 or more doses 6–11 years: 1.2–2.4 g/day in 1 or more doses 12–18 years: 2.4–4.8 g/day in 1 or more doses
<b>Rectal laxatives/enemas</b>	
Bisacodyl	2–10 years: 5 mg/day in 1 dose >10 years: 5–10 mg/day in 1 dose
Sodium lauryl sulfoacetate	1 month–1 year: 2.5 mL/dose (=0.5 enema) 1–18 years: 5 mL/dose (=1 enema)
Sodium docusate	<6 years: 60 mL >6 years: 120 mL
Sodium phosphate	1–18 years: 2.5 mL/kg/dose (maximum 133 mL/dose)
<b>Lubricant</b>	
Mineral oil/liquid paraffin	Oral: 3–18 years: 1–3 mL/kg/day in 1 or more doses (maximum 90 mL/day) Rectal: 2–11 years: 30–60 mL/day in 1 dose; >11 years: 60–150 mL/day in 1 dose

PEG polyethylene glycol

pharmacological treatment options will be discussed below and are summarized in Table 2, including recommended dosages. A treatment algorithm is provided in Fig. 1.

## 4.1 Principles of Pharmacological Treatment

### 4.1.1 Disimpaction

Fecal impaction, defined as the presence of a large fecal mass in the rectum or abdomen, occurs in approximately 50 % of children with FC [25, 46]. Removal of this fecal mass (disimpaction) is recommended prior to initiation of maintenance treatment in order to increase treatment

success [47]. Pharmacological options for disimpaction consist of rectally administered enemas or temporary high-dose oral polyethylene glycol (PEG; 1–1.5 g/kg/day) for 3–6 days (with a maximum of 6 days) [48–50]. One study has compared high-dose PEG and sodium docusate enemas and found these to be equally effective for disimpaction [48]. In comparison with enemas, high-dose PEG is associated with a higher frequency of fecal incontinence during treatment; however, PEG is recommended as the first choice for disimpaction since it can be administered orally and hence is less invasive [15].

### 4.1.2 Maintenance

After successful disimpaction, maintenance therapy should be initiated to prevent re-accumulation of feces [47]. The aim of maintenance treatment is to soften the stools, which facilitates easy and frequent defecation. Several laxatives (oral and rectal), as well as stool softeners, are available for maintenance treatment. Again, PEG is the oral laxative of first choice, in a dosage of 0.2–0.8 g/kg/day. Other therapeutic options are discussed below. Depending on the severity of the symptoms, the effect of treatment should be evaluated 1–2 weeks after initiation of treatment. Maintenance treatment should be continued for at least 2 months, and FC symptoms should be resolved for at least 1 month before weaning is initiated. It is recommended that symptoms are evaluated again 2 months after cessation of treatment, to prevent or detect relapses.

### 4.1.3 Weaning

Approximately 50 % of children with FC on maintenance treatment can stop using their medication within 6–12 months after initiation of treatment [51]. Maintenance medication should be gradually reduced, rather than abruptly discontinued, in order to prevent a relapse [52]. Weaning can be considered when symptoms are stable under maintenance treatment, which means that children have a defecation frequency of  $\geq 3$  times per week and do not fulfill any other Rome III criteria.

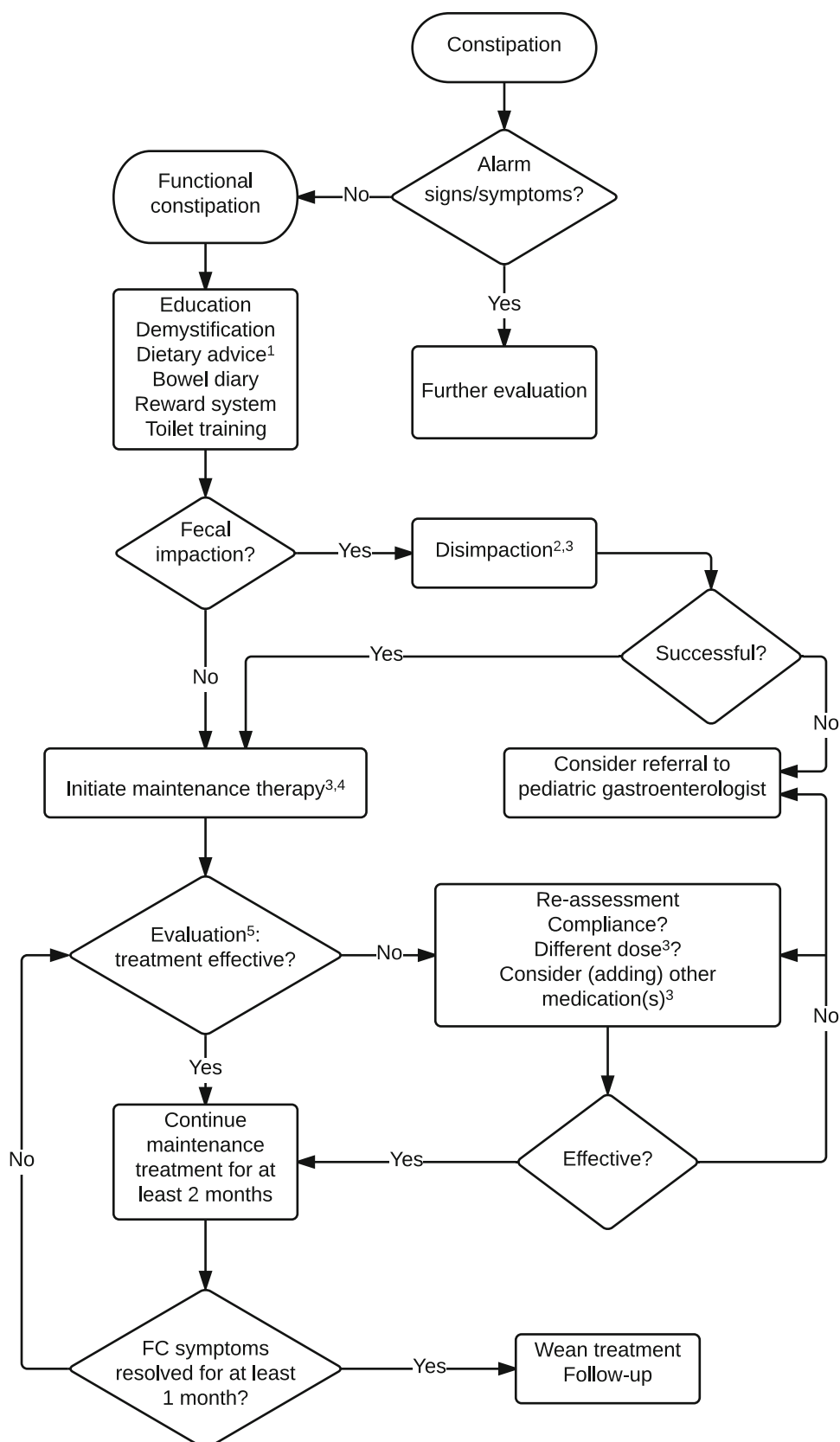
## 4.2 Osmotic Laxatives

Osmotic laxatives are the first step in the pharmacological treatment of FC. They are poorly absorbed by the intestinal wall, which leads to intraluminal accumulation of hyperosmolar particles. This stimulates retention of water in the intestinal lumen, softening the stools and increasing peristalsis through intestinal distension. Furthermore, some osmotic laxatives increase peristalsis through a decrease in intraluminal pH [53]. The most frequently used osmotic laxatives are discussed below.

**Fig. 1** Flowchart of evaluation and management of functional constipation in children.

<sup>1</sup>Ensure adequate fiber and fluid intake. <sup>2</sup>Polyethylene glycol (PEG) is recommended as the first choice for disimpaction.

<sup>3</sup>Medications and dosages can be found in Table 2. <sup>4</sup>PEG is recommended as the first choice for maintenance treatment. <sup>5</sup>The first evaluation should be scheduled after 2 weeks





#### 4.2.1 Polyethylene Glycol

PEG (or macrogol) is the first-choice osmotic laxative in children with FC. It is a linear polymer, in which water molecules are retained by means of hydrogen connections, causing an intraluminal fluid volume increase. It is not metabolized and is minimally (<1 %) absorbed in the intestine [54]. Different types of PEG have been developed—PEG 3350 and PEG 4000, with molecular weights of 3.350 and 4.000 g/mol, respectively. To minimize the risk of disturbing the electrolyte balance by osmosis, a combination of PEG with electrolytes can be used, which is iso-osmotic instead of hypo-osmotic. PEG has been proven to be more effective in increasing stool frequency ( $\geq 3$  times per week) than placebo, lactulose, and magnesium hydroxide in the treatment of constipation [53, 55–57]. The use of PEG is effective and safe, even in young children (aged <2 years) [57–62]. Therefore, PEG is the osmotic laxative of first choice in children with FC. The effect of PEG usually occurs within 1–2 days; when fecal impaction is being treated, this effect might be delayed and may take up to 3 days. Side effects include fecal incontinence (especially during disimpaction), flatulence, abdominal pain, nausea, and abdominal bloating. In patients predisposed to water and electrolyte balance disturbances (patients with impaired hepatic or renal function, or patients taking diuretics), laboratory electrolyte checks should be considered.

#### 4.2.2 Lactulose and Lactitol

Lactulose and lactitol are synthetic derivatives of lactose. These hyperosmolar agents are not hydrolyzed by digestive enzymes in the small intestine and are, for that reason, poorly absorbed by the intestinal mucosa. In the colon, these disaccharides are fermented into hyperosmolar low molecular weight acids by intraluminal bacteria [63]. This results in intraluminal water retention and a decrease in intraluminal pH, which induces an increase in colonic peristalsis. The bacterial fermentation of these agents also leads to formation of gas, which induces additional intestinal distension and increases peristalsis. The effect of lactulose and lactitol is usually observed within a number of days. Side effects of lactulose and lactitol are usually mild and include flatulence, abdominal pain, and abdominal bloating. Chronic use can lead to electrolyte balance disturbances.

Although lactulose is often prescribed to children with FC, evidence supporting the use of lactulose in clinical practice is scarce. Moreover, lactulose has been demonstrated to be less effective than liquid paraffin or PEG in outcomes of stool frequency per week, consistency, relief of abdominal pain, and need for additional medication [53,

55]. No statistically significant difference in treatment success between lactulose and lactitol, lactulose and senna, or lactulose and dietary fiber has been found [53]. Since lactulose is considered to be safe for all ages, it is recommended in case PEG is not available.

#### 4.2.3 Magnesium Hydroxide (Milk of Magnesia)

The antacid magnesium hydroxide (also referred to as “milk of magnesia” in its suspension form) and other magnesium salts (e.g., magnesium sulfate and magnesium citrate) have a laxative effect. This effect is considered to derive from the osmotic gradient that is caused by these poorly absorbed hyperosmolar agents. The effect of magnesium hydroxide occurs after 2–8 h, whereas the effect of magnesium sulfate occurs after 1–3 h. When the effect of PEG on stool frequency per week was compared with that of magnesium hydroxide in children with FC, a statistically significant result was found, favoring PEG [53]. Side effects include diarrhea, hypotension, weakness, and lethargy. Severe renal impairment is a contraindication for the use of magnesium hydroxide.

### 4.3 Stimulant Laxatives

If osmotic laxatives alone prove to be insufficient in the treatment of pediatric patients with FC, stimulant laxatives can be considered as additional or second-line treatment. Stimulant laxatives act directly on the intestinal mucosa, stimulating intestinal motility and/or increasing water and electrolyte secretion. Diphenylmethanes and anthraquinones are stimulant laxatives and are often used in the treatment of FC in children, although literature to support these treatments are lacking [63–65]. Even though abdominal pain is a common side effect, stimulant laxatives are often well tolerated. They are considered to be safe and effective, and can be used in the treatment of FC in children [66].

#### 4.3.1 Diphenylmethanes

Diphenylmethanes include bisacodyl and sodium picosulfate—both non-absorbable agents. In the colon, diphenylmethanes are hydrolyzed to their active metabolites, which exert a local prokinetic effect and stimulate intestinal secretion [63]. Bisacodyl can be administered orally or rectally. The laxative effect of ingested bisacodyl generally occurs within 6–8 h; therefore it is recommended to administer oral bisacodyl ante nocturnum. Rectally administered bisacodyl induces a fast effect (sometimes within 30–60 min). Sodium picosulfate is available only as an oral drug; the time for it to take effect is comparable to that of orally ingested bisacodyl. The most common side effects

are abdominal pain, nausea, and diarrhea. Rectal administration of bisacodyl is contraindicated in children with proctitis or anal fissures.

#### 4.3.2 Anthraquinones

Senna contains a variety of anthraquinones and is metabolized into its pharmacologically active metabolite by intestinal bacteria [63]. This metabolite stimulates colonic motility and secretion of water and electrolytes, while it inhibits absorption of water and electrolytes from the colon. Side effects include abdominal pain, nausea, diarrhea, and flatulence. In young children, senna may potentially cause severe diaper rash, blisters, and skin sloughing, and it should therefore only be used in children aged  $\geq 1$  year [67].

### 4.4 Lubricants

Lubricants are a class of laxatives that mainly soften or lubricate stools.

#### 4.4.1 Mineral Oil

Mineral oil (or liquid paraffin) is a derivative of petroleum. It is not absorbed by the intestines, and it functions as a lubricant. Mineral oil may also exert an osmotic effect when it is converted to fatty acids [65, 68]. It can be administered orally or rectally; the laxative effect generally occurs within 1–2 days for both administration routes.

There have been a few low-quality trials comparing mineral oil with oral laxatives in the treatment of childhood constipation. Two studies compared mineral oil with lactulose [69, 70]; a meta-analysis revealed a significant improvement in stool frequency, although the quality of the evidence was low [53]. Liquid paraffin was also compared with PEG, which revealed no significant difference in treatment response (defined as an increase in bowel movements and a decrease in fecal incontinence frequency) between both groups [71]. In comparison with senna, liquid paraffin was shown to significantly improve the defecation frequency and fecal incontinence episodes; however, the evidence was of low quality [72].

Liquid paraffin is considered to be safe and efficacious in the treatment of FC in children [68]. However, liquid paraffin may leak out of the anus, causing irritation or itching of the skin, and it may stain clothing or furniture. Liquid paraffin can reduce absorption of fat-soluble vitamins (A, D, E, and K), although this is rarely clinically relevant. There have been incidental reports of severe side effects, such as granulomata following absorption, and lipoid pneumonia following aspiration [68, 73, 74]. The

Committee on Safety of Medicines has therefore recommended that liquid paraffin should not be administered to children under 3 years of age [68].

#### 4.4.2 Docusate

Sodium docusate is a mainly rectally administered therapeutic agent, although oral products exist. The surface-active properties of sodium docusate instigate retention of water in the stools, which renders its lubricating effect [63, 75]. There is no evidence that docusate is effective in pediatric patients with FC. Side effects are seldom reported but include diarrhea and rectal discomfort.

### 4.5 Enemas

Enemas are rectally administered fluids, which contain chemically active agents that influence gut motility, agents that exert an osmotic effect, or a combination of both. The effect of enemas is usually seen within minutes after administration. A number of different enemas are used in the treatment of FC in children. Sodium lauryl sulfoacetate brings about a redistribution of the water that is bound to hard feces and exerts a softening effect on feces. This enema does not have an osmotic effect and is usually used in infants. Sodium docusate enemas contain docusate, sometimes with added sorbitol, a hyperosmolar agent that attracts water. Sodium phosphate enemas contain a strong hyperosmolar phosphate solution. PEG and enemas have been proven to be equally effective in achieving disimpaction, but PEG is recommended because of the more invasive nature of enemas [15, 48]. Evidence does not support addition of enemas to chronic use of laxatives in children with constipation [15]. The most common side effects of enemas are abdominal pain and anorectal discomfort. Sodium phosphate enemas are contraindicated if Hirschsprung's disease is suspected, since they have the potential to induce hyperphosphatemia.

### 4.6 Rectal Irrigation

Transanal rectal/colonic irrigation is a procedure where water is infused into the rectum and/or colon to mechanically clean out the intestine. Rectal irrigation was shown to be effective in the management of fecal incontinence due to constipation in children with neurogenic defecation disorders (e.g., spina bifida or Hirschsprung's disease) or anorectal malformations [76–82]. However, data on the effectiveness of transanal irrigation in children with FC are scarce [83]. Irrigations are usually performed with a volume of 10–20 mL/kg of water, with the frequency depending on the patient's response [76, 83].



#### 4.7 Novel Therapies (Lubiprostone, Linaclotide, and Prucalopride)

Lubiprostone, linaclotide, and prucalopride are relatively new drugs, which have been found to be effective in constipated adults [84]. However, data on the efficacy of these agents in the treatment of childhood constipation are scarce or lacking.

Lubiprostone and linaclotide both promote secretion of chloride-rich fluid in the intestine, thereby softening stools and enhancing stool volume. Lubiprostone is a prostaglandin E1 derivative, which activates chloride channel subtype 2 (ClC-2). A pilot study has been conducted, evaluating the effect of lubiprostone in childhood constipation; the results suggested that lubiprostone significantly increases bowel movements and is well tolerated in children and adolescents with FC [85]. Side effects include nausea, vomiting, diarrhea, and abdominal pain [85]. Linaclotide is a synthetic peptide, which activates the luminal guanylin receptor on enterocytes and thereby promotes fluid secretion. To date, no randomized studies on the efficacy of linaclotide have been published in children. In adults, the most frequently reported adverse effect of linaclotide is diarrhea [84, 86, 87].

Prucalopride is a selective, high-affinity 5-hydroxytryptamine (serotonin) receptor 4 agonist, which enhances motility in the gastrointestinal tract [88]. In an open-label, non-controlled, 8-week study, treatment with prucalopride had a favorable effect on stool frequency, stool consistency, and fecal incontinence frequency [89]. However, in a recently published European multicenter double-blind RCT in children with constipation, prucalopride was no more effective than placebo in increasing the stool frequency or decreasing the fecal incontinence frequency. Reported adverse effects include headache, nausea, abdominal pain, and diarrhea [88].

#### 4.8 Probiotics

Over the past decades, advances in culture-independent techniques have led to the discovery that in and on the human body, bacterial cells outnumber human cells by an estimated factor of ten [90–92]. The detection of species that could not be detected previously by culture-based methods has initiated the uncovering of the human microbiome, demonstrating novel concepts that could significantly alter the way we treat disease and promote health in the future [93]. The exact relationship between gut microbiota alterations and FC is still incompletely understood. However, by altering the gut microbiota, probiotics are able to influence colonic motility. Bacterial production of short-chain fatty acids lowers the pH in the colon, which enhances colonic peristalsis and thereby decreases the CTT

[94]. Studies on the use of probiotics have been conducted in children, but, to date, there is insufficient evidence to support the use of probiotics in the treatment of childhood constipation [38, 95].

### 5 Prognosis and Follow-Up

A large proportion of children with FC can be treated effectively with the therapeutic agents that are currently available. Pijpers et al. [51] conducted a systematic review of prospective follow-up studies on the prognosis of FC in the hospital setting (pediatrics and pediatric gastroenterology). On the basis of these largely heterogeneous studies, they concluded that within 6–12 months, approximately 50 % of the children with FC had recovered and were taken off laxatives. An additional 10 % of patients were free of symptoms on medication, and another 40 % would still be symptomatic despite the use of laxatives [51]. After a follow-up period of 5–10 years, 56.0 %  $\pm$  11.3 % of the children had recovered and were no longer taking laxatives. In tertiary care centers, these numbers are similar: 50 % of children referred to a pediatric gastroenterologist have recovered after 5 years, with the vast majority of patients no longer taking laxatives, and after 10 years, 80 % of children have recovered [15]. However, in the remainder of the children, symptoms may persist into adolescence or even adulthood, despite laxative treatment [96–98].

Early adequate therapeutic intervention is of key importance in the management of childhood FC, since a delay between the onset of symptoms and the first presentation at the department of pediatric gastroenterology is negatively related to recovery [98].

In children with severe intractable constipation that is unresponsive to intensive pharmacological treatment, referral to a specialized pediatric gastroenterology and motility center for further evaluation is recommended. In these children, surgical management may be indicated as a treatment of last resort [15, 99].

### 6 Conclusions

Childhood constipation is a common healthcare problem worldwide. The diagnosis is based on the history and a physical examination, in accordance with the Rome III criteria. Additional investigations are required only in situations in which the diagnosis is not clear, and in order to rule out an underlying disease. Non-pharmacological management involves education, demystification, a toilet program with a reward system, and a daily bowel diary. Pharmacological treatment with laxatives consists of

disimpaction, maintenance treatment, and eventually weaning off medication. PEG is the laxative of first choice for both disimpaction (high-dose: 1–1.5 g/kg/day) and maintenance treatment (0.2–0.8 g/kg/day). If PEG is not available or is poorly tolerated, lactulose is recommended. Stimulant laxatives (bisacodyl, senna, sodium picosulfate), magnesium hydroxide, and/or mineral oil may be considered as second-line or additional treatment if treatment with osmotic laxatives is insufficient. Maintenance treatment should be continued for at least 2 months, and FC symptoms should be resolved for at least 1 month before a gradually reduction of the medication. The long-term prognosis is moderate even if early adequate therapeutic interventions are applied.

### Compliance with Ethical Standards

**Conflict of interest** I.J.N. Koppen, L.A. Lammers, M.A. Benninga and M.M. Tabbers declare no conflicts of interest.

**Funding** No sources of funding were used to support the writing of this manuscript.

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